Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Taggart DP, Benedetto U, Gerry S, et al. Bilateral versus single internal-thoracic-artery grafts at 10 years. N Engl J Med 2019;380:437-46. DOI: 10.1056/NEJMoa1808783

Arterial Revascularization Trial (ART)

SUPPLEMENTARY APPENDIX

Page Content

Centres participating in the Arterial Revascularisation Trial (ART). Principal Investigators (shown in bold), co-investigators and co-ordinators (number of patients enrolled).

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2. Medical University of Silesia (2nd Department of Cardiac Surgery), Katowice, Poland**. S Wos, M Jasinski, M Deja**, K Widenka, A Blach, R Gocol, D Hudziak, P Zurek, R Bachowski, R Mrozek, T Kargul, W Domarardzki, J Frackiewicz (256)
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4. Austin and Repatriation Medical Centre, Melbourne, Australia. **B Buxton, S Seevanayagam**, G Matalanis, A Rosalion, J Negri, S Moten, V Atkinson, A Newcomb, P Polidano, R Pana, S Gerbo (192)
5. University Hospital of Wales, Cardiff, UK, **P O'Keefe**, U von Oppell, D Mehta, A Azzu, A Szafranek, E Kulatilake, J Evans, N Martin, D Banner (185)
6. Royal Sussex County, Brighton, UK. **The late A Forsyth, U Trivedi,** J Hyde, A Cohen, M Lewis, E Gardner, A MacKenzie, N Cooter, E Joyce, J Parker, F Champney (180)
7. Freeman Hospital, Newcastle, UK. **S Clark**, J Dark, K Tocewicz, T Pillay, S Rowling, J Adams-Hall (152)
8. Medical University of Silesia (1st Department of Cardiac Surgery), Katowice, Poland. **A Bochenek, M Deja**, M Cisowski, M Bolkowski, W Morawski, M Guc, M Krejca , M Wilczyn-ski, A Duralek, W Gerber, J Skarysz, R Shrestha, W Swiech, P Szmagala, L Krzych, A Pawlak, K Kepa (145)
9. Royal Infirmary, Manchester, UK. **R Hasan**, D Keenan, B Prendergast, N Odom, K McLaugh-lin, G Cummings-Fosong, C Mathew, H Iles-Smith, A Oomen (115)
10. King's College Hospital, London, UK. **J Desai**, A El-Gamel, L John, O Wendler, M Andrews, K Rance, R Williams, V Hogervorst, J Gregory, J Jessup, A Knighton, A Hoare (114)
11. Royal Papworth Hospital, Cambridge, UK. **A Ritchie, C Choong, S Nair, C Sudarshan**, D Jenkins, S Large, M Barman, K Dhital, T Routledge, B Rosengard, H Munday, K Rintoul, E Jarrett, S Lao-Sirieix, A Wilkinson, L Garner, J Osmond, H Holcombe (101)
12. Castle Hill Hospital, Hull, UK. **A Cale**, S Griffin, J Dickson, J Cook (97)
13. Glenfield Hospital, Leicester, UK. **T Spyt, A Gershlick**, M Hickey, A Sosnowski, G Peek, J Szostek, L Hadjinikalaou,, E Logtens, M Oakley, S Leji (95)
14. Harefield Hospital, London, UK. **J Gaer**, M Amrani, G Dreyfus, T Bahrami, F de Robertis, K Baig, G Asimakopoulos, H Vohra, V Pai, S Tadjkarimi, Soleimani, G Stavri, G Bull, H Collappen (94)
15. John Paul II, Krakow, Poland. **J Sadowksi, B Kapelak**, B Gaweda, P Rudzinski, J Stolinski, J Konstanty-Kalandyk, (92)
16. Heart Institute of Pernambuco, Recife, Brazil. **F Moraes**, C Moraes, J Wanderley (82)
17. Royal Brompton Hospital, London, UK. **J Pepper**, A De Souza, M Petrou, R Trimlett, T Morgan, J Gavino, SF Wang (82)

18. St George's Hospital, London, UK. **V Chandrasekaran**, R Kanagasaby, M Sarsam, H Ryan, L Billings, L Ruddick, A Achampong, E Forster, E Mohama, P Mc Donnell (78)
19. Medical University of Gdansk, Gdansk, Poland. **R Pawlaczyk**, P Siondalski, J Rogowski, K Roszak, K Jarmoszewicz, D Jagielak, S Gafka (74)
20. Care Hospital, Hyderabad, India. **G Mannam**, L Rao Sajja, B Raju Dandu, G Naguboyina, A Yalla, J Peddireddy (69)
21. Northern General Hospital, Sheffield, UK. **N Briffa**, P Braidley, G Cooper, A Knighton, K Al-len, G Sangha, C Bridge, H McMellon, P Shaw (67)
22. Ospedale Mauriziano, Turin, Italy. **R Casabona, G Actis Dato,** G Bardi, S Del Ponte, Forsen-nati, F Parisi, G Punta, R Flocco, F Sansone, E Zingarelli, A Demartino (60)
23. The Cardiothoracic Centre, Liverpool, UK. **W Dihmis, M Kuduvali**, C Prince, H Rogers, L McQuade, A Duran-Rosas (50)
24. Szpital Uniwersytecki, Bydgoszcz, Poland. **L Anisimowicz**, M Bokszanski, W Pawliszak, J Kolakowski, G Lau, W Ogorzeja, I Gumanska, P Kulinski (23)
25. Landesklinikum, St Polten and Center for Biomedical Research, Medical University of Vienna, Austria. **B Podesser**, K Trescher, O Bernecker, Ch Holzinger, K Binder, I Schor, P Bergmann, H Kassal, E Dunkel (20)
26. Escorts Heart Institute, New Delhi, India. **N Trehan, Z Meharwal**, R Malhotra, M Goel, B Ku-mer, S Bazaz, N Bake, A Singh, Y Mishka, R Gupta, S Basumatary (19)
27. Silesian Centre for Heart Disease, Zabrze, Poland. **M Zembala**, B Szafron, J Pacholewicz, M Krason, A Farmas, J Wojarski, B Zych, I Jaworska (10)
28. Szpital Wojewodzki 2, Rzeszow, Poland. **K Widenka**, I Szymanik, M Kolwca, W Mazur, A Kurowicki, S Zurek, T Stacel, (6)

Trial Steering Committee

1. Professor P Sleight, Emeritus Professor Cardiovascular Medicine, Oxford, UK (Chairman)
2. The late Professor D Altman, Professor of Statistics in Medicine, Oxford, UK
3. Professor K Channon, Professor of Cardiovascular Medicine, Oxford, UK
4. Professor J Dark, Professor of Cardiac Surgery, Newcastle, UK
5. Ms B Farrell, Trials Director, National Perinatal Epidemiology Unit, Oxford,
6. Dr M Flather, Professor of Medicine and Clinical Trials, Norwich, UK
7. Professor A Gray, Professor of Health Economics, Oxford, UK
8. Professor J Pepper, Professor of Cardiac Surgery, London, UK
9. Dr R Stables, Consultant Cardiologist, Liverpool, UK
10. Professor D Taggart Consultant Cardiac Surgeon, Oxford, UK (Chief Investigator)
11. The late Professor G Vermes, Emeritus Professor of Hebrew Studies, Oxford, UK (Patient Lay Member)
12. Professor J Pearson British Heart Foundation, London, UK (Observer)
13. Dr M Pitman, Medical Research Council, London, UK (Observer)
14. Mrs J Cook, Research Nurse, Oxford UK (Observer)
15. Mrs C Wallis, Trial Administrator and Manager, Oxford UK (Observer)
16. Dr B Lees, Trial Manager, Oxford UK (Observer)

Data Monitoring Committee

1. Professor S Yusuf, Professor of Medicine, Hamilton, Canada (Chairman)
2. Professor S Pocock, Professor of Medical Statistics, London, UK
3. Professor D Julian, Emeritus Professor of Cardiology, London, UK
4. Professor T Treasure, Professor of Cardiothoracic Surgery, London, UK

Clinical Event Adjudicators

1. Mr U Trivedi, Royal Sussex County Hospital, Brighton, UK
2. Mr P O'Keefe, University Hospital of Wales, Cardiff, UK
3. Professor U Von Oppel, University Hospital of Wales, Cardiff, UK
4. Mr V Zamvar, Edinburgh Royal Infirmary, Edinburgh, UK
5. Mr A Cale, Castle Hill Hospital, Hull, UK
6. Mr M Hickey, Glenfield Hospital, Leicester, UK
7. Mr T Spyt, Glenfield Hospital, Leicester, UK
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10. Mr T Pillay, Freeman Hospital, Newcastle, UK
11. Mr P Braidley, Northern General Hospital, Sheffield, UK
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13. Professor M Flather, University of East Anglia, Norwich, UK
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15. Dr A Bakhai, Barnet General Hospital, Barnet, UK
16. Dr R Pawlaczyk, Medical University Of Gdansk, Gdansk, Poland
17. Dr R O'Hanlon, Royal Brompton Hospital, London, UK

18. Dr D Kotecha, University of Birmingham, Birmingham UK
19. Dr K Qureshi, London Chest Hospital, London, UK
20. Professor L Krzych, Medical University Of Silesia, Katowice, Poland
21. Professor T Geisler, University Hospital Tuebingen, Tuebingen, Germany
22. Mr N Briffa, Northern General Hospital, Sheffield, UK
23. Professor L Manzano-Espinosa, Hospital Universitario Ramon y Cajal Madrid, Spain
24. Professor M Jasinski, Department Cardiac and Thoracic Surgery, Wroclaw Medical University, Poland

Definitions of Outcome Events used in ART

Adjudication method

Two members of the clinical event review committee adjudicated each event (death, myocardial infarction, stroke and re-intervention) in a blinded fashion to ensure events met the pre-specified protocol definitions. If the two adjudicators did not concur, then the event was adjudicated by a third adjudicator to reach resolution. All other adverse events requiring or prolonging hospitalisation were adjudicated by one member of the committee.

1. Death

(a) Death due to cardiac causes:
Cardiac causes of death such as congestive heart failure, arrhythmia or myocardial infarction.
(b) Other vascular causes of death:
Vascular causes of death such as pulmonary embolus, dissection, cerebrovascular accident or bleeding event.
(c) Non-cardiovascular causes of death:
This includes any other cause of death.

2. Major Bleed

A major bleeding event is defined as requiring the use of blood products or a surgical procedure to deal with the bleed or its sequelae.

3. Cerebrovascular Accident (CVA)

A CVA is defined as a new focal neurological deficit thought to be vascular in origin with signs and symptoms lasting more than 24 hours.

4. Revascularization

For the purpose of the trial a revascularization is described as a Coronary Artery Bypass Graft (CABG) or Percutaneous Coronary Intervention (PCI) after the trial procedure.

5. Myocardial Infarction (MI)

(a) Non peri-procedural MI

MI definition (2 out of the following 3 criteria must be present)

- New onset or worsening pattern of characteristic ischemic chest pain occurring at rest or with minimal exercise lasting longer than 20 minutes and requiring nitrates or narcotic analgesia for relief of pain.
- Elevation of cardiac markers (CK, CK-MB or Troponin) to at least twice the upper limit of the normal reference range (or greater than 20% of the previous value if already elevated in the context of early hospital MI).
- ECG changes compatible with ischemia.

(b) MI within 48 hours of PTCA
MI post-PTCA defined as:

- the standard as above (at least 2 of 3 criteria)

or

- elevation of cardiac markers to at least 3 x the upper limit of normal.

(c) MI within 72 hours of CABG
MI post-CABG defined as:

- elevation of cardiac markers to at least 5 x the upper limit of normal

or

- development of new pathological Q waves in at least two contiguous leads.

Other Serious Adverse Events

A "Serious Adverse Event" (SAE) is defined as requiring or prolonging hospital admission for medical reasons. The hospitalization does not have to be related to the study procedure or patient's underlying cardiovascular disease for it to constitute an "Other SAE".

Quality of Life
Quality of life was assessed using the shortened World Health Organization Rose angina questionnaire, the European Quality of Life–5 Dimensions (EQ-5D) questionnaire and the Medical Outcomes Study 36-Item Short-Form Health Survey (SF-36). Quality of life data are reported separately.

Table S1: Additional baseline demographic and clinical characteristics by randomized group

	Bilateral graft group (n=1548)	**Single graft group (n=1554)**
Ethnic origin [n (%)]		
Caucasian	1418 (91.6%)	1431 (92.1%)
East Asian	5 (0.3%)	1 (0.1%)
South Asian	74 (4.8%)	76 (4.9%)
Afro-Caribbean	0	2 (0.1%)
African	4 (0.3%)	1 (0.1%)
Other	47 (3.0%)	42 (2.7%)
Missing	0	1
NYHA class [n (%)]		
I	481 (31.1%)	481 (31.0%)
II	722 (46.6%)	747 (48.1%)
III	279 (18.0%)	263 (16.9%)
IV	66 (4.3%)	61 (3.9%)
Missing	0	2
CCS class [n (%)]		
0	132 (8.5%)	128 (8.2%)
I	348 (22.5%)	355 (22.8%)
II	582 (37.6%)	598 (38.5%)
III	368 (23.8%)	351 (22.6%)
IV	118 (7.6%)	122 (7.9%)

CCS = Canadian Cardiovascular Score. NYHA = New York Heart Association;

Table S2: Details of surgical procedure, post-operative care and hospital stay

Procedures	**Bilateral graft group**	**Single graft group**
Details of operation	(n=1531)	(n=1546)
On pump	890 (58.1%)	928 (60.0%)
Off pump	641 (41.9%)	618 (40.0%)
Intra-operative conversions to cardiopulmonary bypass	15/641 (2.3%)	13/618 (2.1%)
Mean (SD) duration of operation, mins	222 (61)	199 (58)
Median (IQR)	215 (185 to 250)	190 (160 to 250)
Number of vessels grafted	(n=1530)	(n=1546)
1	8 (0.5%)	11 (0.7%)
2	272 (17.8%)	273 (17.7%)
3	771 (50.4%)	749 (48.5%)
4+	479 (31.3%)	513 (33.2%)
Radial artery graft	300 (19.4%)	339 (21.8%)
Blood products used during surgery		
Aprotinin started during surgery	368/1531 (24.0%)	372/1545 (24.1%)
Aprotinin given after surgery	98/1530 (6.4%)	89/1545 (5.8%)
Blood transfusion	179/1492 (12.0%)	184/1515 (12.2%)
Median (IQR) blood (red cells)	500 (300 to 600)	500 (300 to 600)
Platelets	46/1494 (3.1%)	35/1512 (2.3%)
Fresh Frozen Plasma (FFP)	66/1493 (4.4%)	53/1513 (3.5%)
Cell saver	461/1479 (31.2%)	474/1500 (31.6%)
Immediate post-operative period		
Return to theatre and reason	66/1532 (4.3%)	54/1546 (3.5%)

Bleeding	*51*	*44*
Tamponade	*6*	*2*
Other	*9*	*8*
Unknown	*6*	*3*
Intra-aortic balloon pump used (IABP)	68/1532 (4.4%)	57/1546 (3.7%)
Renal support therapy	91/1532 (5.9%)	68/1545 (4.4%)
	(n=1524)	(n=1539)
Mean (SD) Duration of ventilation (minutes)	968 (3029)	863 (3293)
Median (IQR)	598 (360 to 890)	580 (335 to 830)
Pre-discharge details	(n=1429)	(n=1447)
ITU admissions: 0	8 (0.6%)	8 (0.6%)
1	1362 (95.3%)	1390 (96.1%)
2 or more	59 (4.1%)	49 (3.4%)
	(n=1538)	(n=1551)
Mean (SD) ITU length of stay (hours)	41 (94)	38 (106)
Median (IQR)	22 (15 to 45)	22 (16 to 43)
Mean (SD) HDU length of stay (days)	2 (3.8)	2 (3.7)
Median (IQR)	1 (1 to 2)	1 (1 to 2)
Mean (SD) post-operative total hospital stay (days)	8.0 (7.4)	7.5 (7.6)
Median (IQR)	6.5 (5 to 8)	6 (5 to 8)

ITU = intensive therapy unit; HDU = high dependency unit, IQR = interquartile range

Table S3: Medications at 10 years

Medication (%)	Bilateral graft group (n=1075)	Single graft group (n=1046)
Aspirin	81.9%	80.1%
Clopidogrel	13.7%	15.3%
Warfarin	6.9%	6.3%
Other anticoagulant	3.5%	4.4%
Beta-blockers	71.8%	75.9%
Calcium-channel antagonist	21.4%	20.8%
Nitrates	12.9%	11.9%
Potassium channel activators	4.1%	3.9%
Statins	89.6%	91.2%
Other lipid lowering agent	1.4%	1.3%
ACE inhibitor	56.3%	55.6%
Angiotensin-II antagonist	16.4%	16.7%
Diuretics	19.6%	19.7%
Digoxin	1.3%	2.2%
Amiodarone	0.8%	0.9%

Medication information is provided for those with complete case report form data at 10 years.

Table S4: Classification of causes of death

Cause of death n (%)	Bilateral graft group (n=1548)	Single graft group (n=1554)	Subdistribution Hazard Ratio (95% CI)
Cardiac	92 (5.9%)	91 (5.9%)	1.01 (0.76, 1.35)
Non-cardiovascular	152 (9.8%)	160 (10.3%)	0.95 (0.76, 1.19)
Other vascular	20 (1.3%)	28 (1.8%)	0.72 (0.40, 1.27)
Unable to classify	51 (3.3%)	50 (3.2%)	1.02 (0.69, 1.51)

Hazard ratios use the single graft group as the control. The widths of the confidence intervals have not been adjusted for multiplicity and should not be used for inference.

Table S5: Per protocol analyses (comparison based on patients who actually received randomly assigned treatment)

Outcome	Bilateral graft group n	Single graft group n	Deaths Bilateral graft group n (%)	Deaths Single graft group n (%)	Hazard Ratio (95% CI)
Primary ITT unadjusted	1548	1554	315 (20.3%)	329 (21.2%)	0.96 (0.82, 1.12)
Primary ITT adjusted[1]	1548	1554	315 (20.3%)	329 (21.2%)	0.97 (0.83, 1.14)
Per protocol unadjusted	1294	1494	255 (19.7%)	317 (21.2%)	0.92 (0.78, 1.08)
Per protocol adjusted[1]	1294	1494	255 (19.7%)	317 (21.2%)	0.96 (0.81, 1.13)

Adjusted for age, gender, diabetes and ejection fraction[1]
Hazard ratios use the single graft group as the control. The widths of the confidence intervals have not been adjusted for multiplicity and should not be used for inference.
ITT= Intention to treat

Table S6: Baseline characteristics: as treated analysis of multiple (2 or more) arterial grafts versus single arterial graft

	Multiple (2 or more) arterial grafts	**Single arterial graft**	**P**
n	1690	1330	
Female n (%)	232 (13.7)	194 (14.6)	0.535
Age mean years (SD)	63.1 (8.9)	64.2 (8.9)	0.001
Smoking (%)			0.007
Current smoker	257 (15.2)	170 (12.8)	
Ex-smoker	908 (53.7)	790 (59.4)	
Never smoked	525 (31.1)	370 (27.8)	
Ethnicity (%)			0.224
Caucasian	1552 (91.8)	1221 (91.9)	
East Asian	5 (0.3)	0 (0.0)	
South Asian	79 (4.7)	66 (5.0)	
Afro-Caribbean	2 (0.1)	0 (0.0)	
African	4 (0.2)	1 (0.1)	
Other	48 (2.8)	41 (3.1)	
Height mean cm (SD)	170.6 (8.5)	169.9 (8.4)	0.020
Weight mean kg (SD)	82.6 (13.8)	81.1 (13.9)	0.003
Body Mass Index mean (SD)	28.4 (4.0)	28.0 (4.0)	0.035
Systolic blood pressure mean mmHg (SD)	131.8 (18.2)	131.9 (18.3)	0.777
Diastolic blood pressure mean mmHg (SD)	75.0 (11.2)	75.0 (10.9)	0.908
Diabetes (%)			0.262

No history	1285 (76.0)	1019 (76.6)	
Insulin dependent diabetes	104 (6.2)	64 (4.8)	
Non-insulin dependent diabetes	301 (17.8)	247 (18.6)	
Treated Hypertension n (%)	1293 (76.5)	1059 (79.6)	0.045
Treated Hyperlipidemia n (%)	1583 (93.7)	1251 (94.1)	0.760
Peripheral arterial disease n (%)	120 (7.1)	93 (7.0)	0.965
Transient ischemic attack n (%)	51 (3.0)	56 (4.2)	0.096
Cerebrovascular accident n (%)	50 (3.0)	39 (2.9)	1.000
Myocardial infarction n (%)	672 (39.8)	589 (44.3)	0.015
Percutaneous Coronary Intervention n (%)	258 (15.3)	217 (16.3)	0.470
New York Heart Association Class (%)			0.934
missing	1 (0.1)	1 (0.1)	
I	517 (30.6)	422 (31.7)	
II	814 (48.2)	619 (46.5)	
III	290 (17.2)	234 (17.6)	
IV	68 (4.0)	54 (4.1)	
Canadian Cardiovascular Society Class (%)			0.001
0	153 (9.1)	101 (7.6)	
I	427 (25.3)	258 (19.4)	
II	609 (36.0)	537 (40.4)	
III	369 (21.8)	335 (25.2)	
IV	132 (7.9)	99 (7.5)	

Table S7: As treated analysis comparing multiple (2 or more) arterial grafts with single arterial graft: outcomes at 10 years

	Multiple (2 or more) arterial grafts	**Single arterial graft**	**Adjusted HR [95% CI]**
n	1690	1330	
All-cause death n (%)	315 (18.6)	307 (23.1)	0.81 [0.68-0.95]
Myocardial Infarction n (%)	79 (4.7)	64 (4.8)	0.84 [0.59-1.19]
Stroke n (%)	64 (3.8)	66 (5.0)	0.76 [0.53-1.11]
Repeat revascularization n (%)	169 (10.0)	136 (10.2)	0.89 [0.70-1.14]
All-cause death, myocardial infarction or stroke n (%)	399 (23.6)	385 (28.9)	0.80 [0.69-0.93]

The widths of the confidence intervals have not been adjusted for multiplicity and should not be used for inference.

Figure S1: Rates of patients randomized to bilateral internal-thoracic-artery graft who actually received single internal-thoracic-artery graft stratified by total number of cases performed by surgeon. The blue line represents regression line using polynomial spline function (information on participating surgeon was not available for 156 patients).

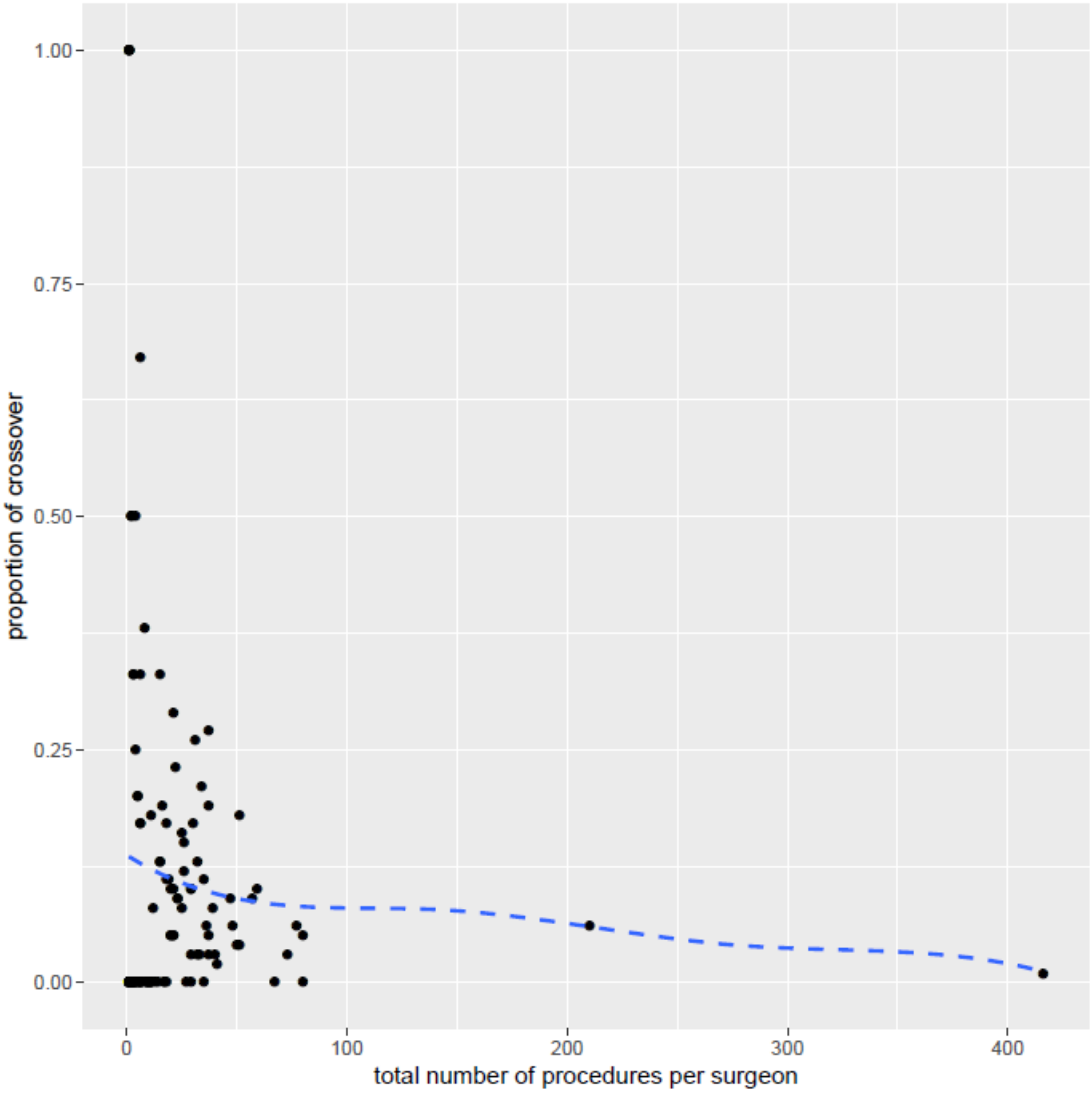
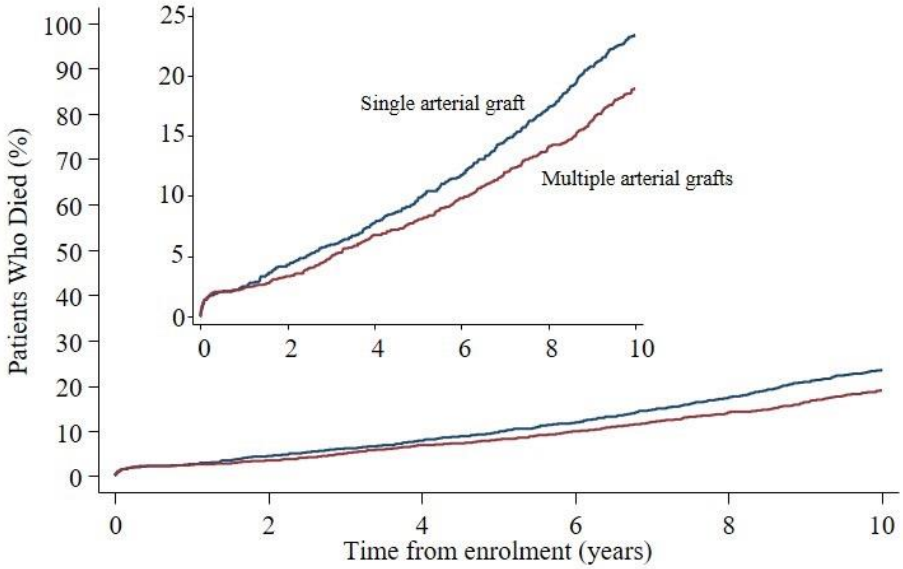


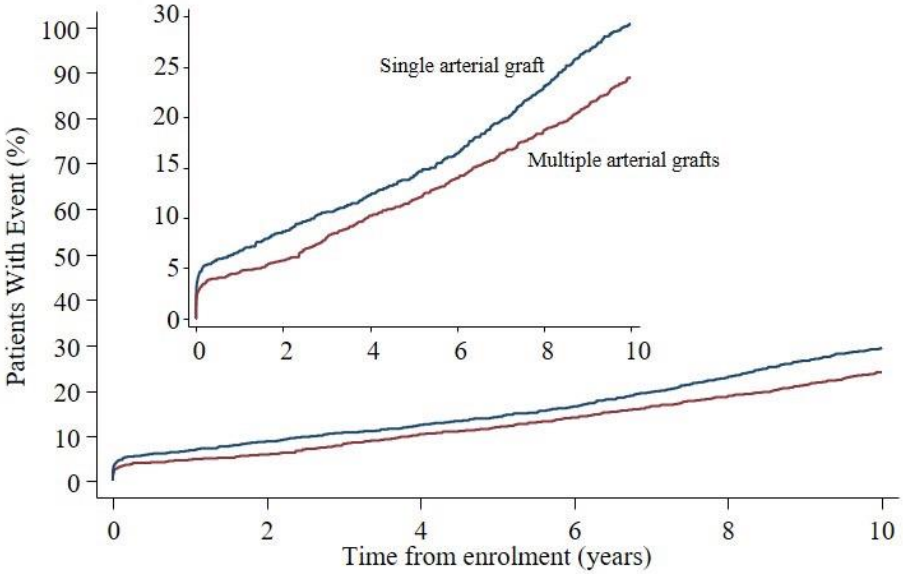
Figure S2 Panel A: As treated analysis of multiple (2 or more) arterial grafts versus single arterial graft (mortality). Adjusted HR 0.81; 95% CI 0.68-0.95



No. at Risk

Multiple arterial grafts	1690	1632	1567	1510	1430	998
Single arterial graft	1330	1270	1222	1163	1081	750

Figure S2 Panel B: As treated analysis of multiple (2 or more) arterial grafts versus single arterial graft (all-cause mortality, myocardial infarction or stroke). Adjusted HR 0.80 95% CI 0.69-0.93



No. at risk

Multiple arterial grafts	1690	1591	1510	1442	1353	934
Single arterial graft	1330	1212	1162	1101	1006	691